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Introduction

The brain derives its energy from the oxidation of glucose in the normal in vivo state. In human beings as well as various experimental animals, positive arterio-venous difference (arterial minus venous concentration of substrate) of glucose and oxygen and negative difference of carbon dioxide is generally found.[19] Cerebral glucose uptake is tightly coupled with oxygen consumption in oxygen-rich cerebral tissue. Therefore, the change in cerebral metabolic ratio of oxygen to glucose might imply some metabolic failure of energy production in the brain.

By measuring cerebral blood flow (CBF) based on the Kety-Schmidt method[8] and arterio-venous difference of glucose and oxygen, the ratio of cerebral oxygen consumption ($CMRO_2$) to cerebral glucose utilization (CMRGlc) obtained in normal and diseased human beings.[4),8b] Using positron emission tomography (PET), regional CBF and $CMRO_2$ can be measured with oxygen-15 inhalation.[24] Local CMRGlc is estimated with PET and 2-deoxy-[^{18}F]2-fluoro-D-glucose (^{18}FDG).[13,14] When oxygen-15 inhalation technique is combined with ^{18}FDG method, we are able to evaluate regional changes of the metabolic ratio of oxygen to glucose in various pathological conditions.[1,5,16,20]

Although the values of oxygen/glucose utilization ratio for normal volunteers using PET were reported by some groups, these values were lower than those obtained by the Kety-Schmidt method.[3,5,17] In the present study, we measured the regional cerebral metabolic ratio of oxygen to glucose using positron emission tomography and oxygen-15 steady-state inhalation combined with ^{18}FDG method in normal controls. The metabolic ratios ($CMRO_2$/CMRGlc) obtained for cortical gray matter, basal ganglia and white matter were compared with the reported value for a whole brain by the Kety-Schmidt method.

Materials and Methods

Six normal controls were studied at Cyclotron and Radioisotope Center, Tohoku University between September 1983 and March 1987. There were four males and three females with a mean age of 62(52 or 71). The diagnosis of CNS normality was based on the clinical examination and psychological testing as

well as computed tomography. During the PET study the physiological factors were measured and summarized in Table 1. The subject's informed consent was obtained before the study.

The subjects were scanned with the single plane ECAT II using medium resolution shadow shield to give a resolution of 15 mm in the tomographic plane and 18 mm slice thickness. A cross of light was projected onto marks on subject head from three dimentions. Before scanning, a short 21-gauge cannula was inserted to brachial or radial artery for arterial blood sampling. All the procedures were performed in the semi-darkened room. The subject's eyes were closed.

Cerebral blood flow was measured at 50 and 70 mm above and parallel to orbito-meatal line by inhaling oxygen-15 labeled carbon dioxide ($C^{15}O_2$) 10 to 15 m Ci per minute, and oxygen extraction fraction (OEF) by inhaling oxygen-15 labeled molecular oxygen ($^{15}O_2$) 15 to 20 mCi continuously. Both of $C^{15}O_2$ and $^{15}O_2$ were transported to patient face mask via radioactive gas supply system (Hoxan co., Sapporo and Anzai Sogyo Co., Tokyo). Arterial blood samplings were performed at least twice, usually three times in a scanning. Radioactivity of whole blood and plasma was measured using well counter cross-calibrated with PET scanner. Arterial partial pressure of oxygen and carbon dioxide as well as hemoglobin concentration was estimated. Regional CBF, OEF and $CMRO_2$ was calculated according to Frackowiack et al.[24] The partition coefficient of water (ml blood/ml brain) in the model employed was 1.04 for cerebral cortex and 0.88 for centrum semi-ovale. The partition coefficient of basal ganglia was 0.96, the mean for caudate nucleus and thalamus.[7] In the present protocol, the measurement of cerebral blood volume (CBV) was not included. To correct the known inaccuracy of OEF, the mean value of CBV measured with C-11 monoxide[12] in eight age-matched normal controls in our center, 4.1 % for cortex, 3.0 % for basal ganglia and 2.0 % for centrum semiovale was applied to each patient.

After the decay of oxygen-15 distributing in the brain and blood, up to 5 mCi of ^{18}FDG was administrated to each subject intravenously. Repeated scanning at 50 mm above and parallel to orbito-meatal line started at the beginning of ^{18}FDG administration. Ten sequential images with 5 minutes data aquisition were obtained at this level. After the sequential scanning, the additional image at OM + 70 mm was obtained. During the scanning, arterial blood samplings were taken periodically. These blood samples were centrifuged and arterial plasma radioactivity of ^{18}FDG was measured with cross-caliblated well counter. Arterial plasma glucose concentration of samples taken every ten minute were estimated. CMRGlc was calculated based on the Sokoloff model [,21], using kinetic rate constants for FDG determined by Phelps et al.[13], and a lumped constatnt of 0.52 measured by Reivich et al[15] in normal volunteers. Before the emission scanning, a transmission scan using ^{68}Ge-^{68}Ga external ring source was performed. All the emission data were corrected for attenuation using transmission data.

Square regions of interest were put on frontal, temporal, occipital and parietal cortex, basal ganglia and centrum semiovale shown in Figure 1. The mean values of fourteen regions of interest in various cortical area (seven for each hemisphere), the mean values of right and left basal ganglia and the mean values of right and left centrum semiovale were calculated in each subject. In the subjects of #194 and #312, the cross sectional images of 70 mm above orbito-meatal line included lateral ventricles and partly centrum semiovale. The analysis for centrum semiovale in the cases was not performed.

Results

Table 2 summarized the values of CBF, $CMRO_2$ CMRGlc and cerebral metabolic ratio ($CMRO_2$/CMRGlu) in molecular unit for cortical gray matter, basal ganglia and centrum semiovale (white matter). There was no significant difference of the $CMRO_2$/CMRGlc between basal ganglia and white matter. The cortical value of the $CMRO_2$/CMRGlc was significantly lower than that of white matter. Assuming that gray matter has 4 times higher metabolic rate and that gray-white matter volume ratio is 50:50 for whole brain, we obtained whole brain $CMRO_2$/CMRGlc of 5.0 using the $CMRO_2$/CMRGlc value for cortical gray matter and for centrum semiovale, 5.53 using the $CMRO_2$/CMRGlc value for basal ganglia and for centrum semiovale.

Discussion

Cerebral metabolic ratio ($CMRO_2$/CMRGlc) has been intensively studied with the Kety-Schmidt method for a whole brain. When one molecular glucose is completely oxidized and the glucose is the sole substrate for oxidative metabolism, the expected oxygen consumption should by 6 mole and the carbon dioxide and water might be the end-product. In normal resting human brain, the $CMRO_2$/CMRGlc measured for a whole brain was around 5.5 in molecular unit indicating almost 90 % of glucose is oxidized and some alternative glucose metaboliosm might exist.[4,9,18,23]

Using PET, the regional $CMRO_2$/CMRGlc was measured by some groups. Rhodes et al.[16] demonstrated uncoupling between glucose and oxygen metabolism in human brain tumors. Wise et al.[20] and Baron et al.[1,2] documented local alternation of oxidative metabolism of glucose in patients with cerebral infarction. However, the absolute value of $CMRO_2$/CMRGlc measured in normal volunteers with PET was unexpectedly lower than that of the Kety-Schmidt method. For example, Baron et al.[3] reported the $CMRO_2$/CMRGlc of 4.58 with LC= 0.42, the blood-brain partition coefficient for water of 0.96 and no blood volume correction for OEF estimation. Hatazawa et al.[5] obtained the cortical value of 3.82 with LC=0.42, no washout correction of brain FDG and no blood volume correction. Sasaki et al.[17] recently reported the $CMRO_2$/CMRGlc value of 4.38 in the cortex using individual rate constants measurement in FDG study, LC=0.52 and with blood volume correctin for OEF.

PET measurement of $CMRO_2$ and CMRGlc based on the completely different methodology from the Kety-Schmidt technique. The $CMRO_2$/CMRGlc values obtained by PET depends on the model parameters employed for the quantitation such as the lumped constant, the rate constants in the FDG model and the partition coefficient for water in the CBF measurement.

In the CMRGlc measurement with PET and ^{18}FDG, we are first measuring ^{18}FDG concentration is converted to glucose utilization rate. Phelps et al.[13] used the model lumped constant of 0.42 to ajust the ^{18}FDG concentration to the whole brain CMRGlc obtained by the Kety-Schmidt method. Reivich et al.[15] directly determined the extraction ratio of ^{18}FDG to glucose in the whole brain by measuring arterio-venous difference of ^{18}FDG and glucose in normal volunteers. The obtained value of 0.52 was validated independently using PET-FDG data by Brooks et al.[22].

In the oxygen-15 steady state inhalation for the determination of CBF, OEF and $CMRO_2$, the blood-brain partition coefficient for water might affect CBF value and accordingly $CMRO_2$. Regional CBF is usually calculated using the mean partition coefficient for gray and white matter. However, as Herscovich et al.[7] pointed out, the partition coefficient is different among brain structures depending on the water content. For example, the partition coefficient (ml/g) should be 0.99 for cortical gray matter, 0.88 for thalamus and 0.83 for centrum semiovale. Another error source of $CMRO_2$ might be the existence of the blood in cerebral vasculature. This would cause overestimation of OEF even in normal volunteers.[11]

Considering the problems mentioned above, we calculated CMRGlc using standard set of rate constants for gray matter in cortex and basal ganglia reported by Phelps et al.[12], the model lumped constant of 0.52 measured by Reivich et al.[15]. CBF was obtained using the partition coefficient (ml/ml) of 1.04 for cortical gray matter and 0.87 for centrum semiovale. The mean partition coefficient for thalamus and caudate nucleus was employed for basal ganglia. Although the present subject population did not have CBV measurement, we applied the mean CBV value for cortex, basal ganglia and centrum semiovale of another age-matched population to correct overestimation of OEF.

The mean $CMRO_2$/CMRGlc values of 5.8 for centrum semiovale and 5.46 for basal ganglia obtained in the present study were in close agreement with the Kety-Schmidt value. However, the $CMRO_2$/CMRGlc of 4.84 for cortical gray matter was almost 10 % lower than the Kety-Schmidt value. We consider that this difference was induced by the inaccuracy of the PET measurement rather than physiological significance. Low spacial resolution in the present PET scanner inevitably disturb the accurate estimation of ^{18}FDG and $H_2{}^{15}O$ concentration in heterogeneous region. If radioactivity in the tissue linearly correlates with physiological parameters, inaccuracy induced by partial volume effect might be canceled by taking the ratio of two images. However, Lammertsma et al.[10] predicted a maximum 18 % underestimation of flow

in a 50:50 grey-white matter region of interest considering the effect of only flow heterogeneity. Herscovich et al.[6] reported the same or higher magnitude of flow underestimation when partition coefficient for water was taken into account. In contrast, the tissue heterogeneity might not be serious error source for the CMRGlc determination. In the Brooks's equation, ^{18}FDG concentration in the tissue linearly correlated with CMRGlc. Therefore, the mean CMRGlc ontained from the mean ^{18}FDG concentration of gray and white matter might be close to the mean of CMRGlc for gray and white matter. Low $CMRO_2$/CMRGlc value in the cortical region might be induced by the heterogeneity problem to some extent.

Whether the regional difference of $CMRO_2$/CMRGlc exists or not is the question the PET study should answer. There was no significant difference of the $CMRO_2$/CMRGlc between the white matter(centrum semiovale) and the grey matter in the basal ganglia. This result could be interprited that glial cell rich region (centrum semiovale) and neuron rich-region (basal ganglia) have similar nature of in vivo oxidative metabolism of glucose.

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Table 1. Physiological information of normal controls at the PET study.

	n = 7
age (years)	62 ± 6
systolic blood pressure (mm Hg)	133 ± 17
diastolic blood pressure (mm Hg)	81 ± 10
hemoglobin (g/dl)	13.8 ± 1.7
arterial oxygen content (ml O_2/ml blood)	0.176 ± 0.025
PaO_2 (mm Hg)	86.3 ± 5.9
$PaCO_2$ (mm Hg)	40.9 ± 2.4
Plasma glucose concentration (mg/dl)	110 ± 16

PaO_2; arterial partial pressure of O_2
$PaCO_2$; arterial partial pressure of CO_2

Table 2. CBF, $CMRO_2$, CMRGlc and $CMRO_2$/CMRGlc in the cortex, basal ganglia and centrum semiovale.

cortical gray matter

	CBF (ml/100g/min)	$CMRO_2$ (ml/100g/min)	CMRGlc (ml/100g/min)	$CMRO_2$/CMRGlc (mol/mol)
# 114	40.8	2.32	4.68	5.06
# 194	45.0	3.95	6.24	5.08
# 210	37.8	2.86	4.31	5.32
# 270	50.2	3.33	5.20	5.14
# 271	42.3	3.62	5.80	5.03
# 278	47.9	2.58	3.73	4.38
# 312	45.5	3.25	6.20	4.20
mean	44.2	3.13	5.17	4.89
1 SD	4.2	0.88	0.98	0.42

basal ganglia

	CBF (ml/100g/min)	$CMRO_2$ (ml/100g/min)	CMRGlc (ml/100g/min)	$CMRO_2$/CMRGlc (mol/mol)
# 114	49.6	2.63	3.71	5.69
# 194	59.2	4.89	5.92	6.63
# 210	38.8	2.90	4.31	5.40
# 270	50.0	2.40	5.20	3.71
# 271	44.7	3.74	5.09	5.90
# 278	57.9	3.09	4.82	5.14
# 312	50.5	2.99	5.42	4.43
mean	44.2	3.13	5.17	5.27
1 SD	7.1	0.84	0.73	0.97

centrum semiovale

	CBF (ml/100g/min)	$CMRO_2$ (ml/100g/min)	CMRGlc (ml/100g/min)	$CMRO_2$CMRGlc (mol/mol)
# 114	30.8	1.76	2.26	6.24
# 210	26.7	2.06	2.90	5.70
# 270	28.1	2.00	3.30	4.85
# 271	25.4	1.92	2.80	5.50
# 278	32.2	1.79	2.10	6.82
mean	28.6	1.91	2.67	5.82
1 SD	2.9	0.13	0.49	0.75

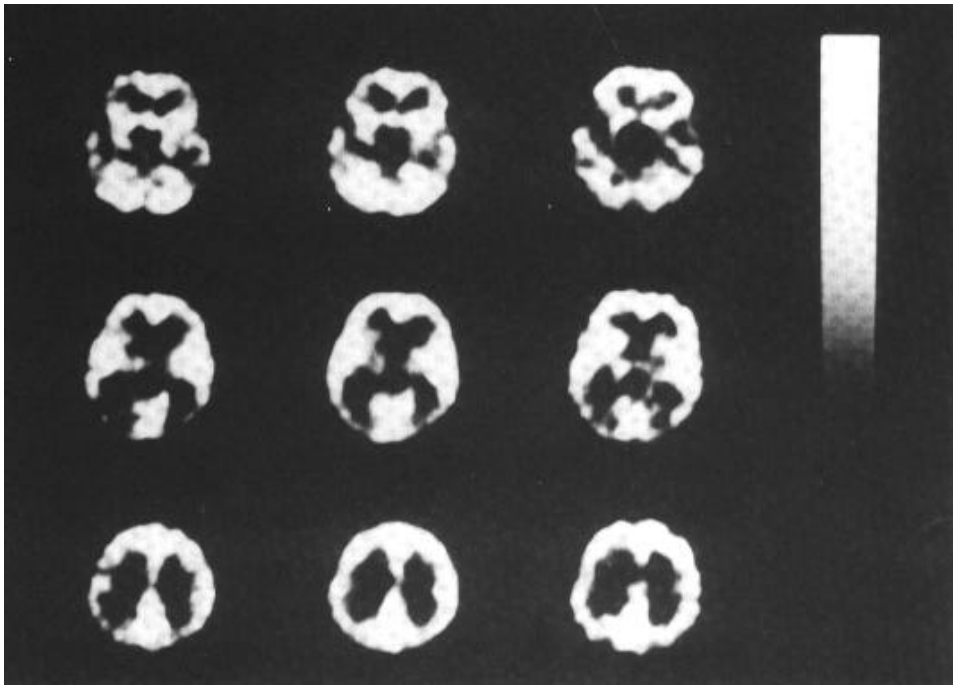

Fig. 1. PET images of CBF(right column), $CMRO_2$ (center column) and CMRGlc(left column). Upper row was obtained in OM+70 mm, CBF images were reconstructed with partition coefficient of 0.99 for water. CMRGlc images were obtained with the Brooks equation using rate constants for gray matter and the lumped constant of 0.52.